Telemedicine in heart failure: New insights from the Cochrane meta-analyses.

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During his visit to Florence in 1817 the French author Stendhal experienced sudden palpitations, dizziness and confusion on beholding the vast amount of magnificent artwork. This phenomenon was later called the Stendhal syndrome. Nowadays, physicians are prone to a certain kind of Stendhal syndrome when facing the massive amount of papers being published worldwide. Selection of interesting and reliable manuscripts is important, but the true challenge lies in making sense of all results, especially when conflicting data emerge.

The Cochrane Collaboration was founded in 1993 in response to a call from an epidemiologist, Archie Cochrane, for up-to-date, systematic reviews or 'critical summaries' of all relevant randomized controlled trials (RCT) of health care interventions. Using stringent guidelines, the Cochrane Collaboration collects data on a specific research topic and establishes whether there is conclusive evidence of utility for a treatment or intervention. Cochrane reviews are recognized by many as the highest standard in evidence-based health care resources.

In 2007, the first Cochrane review on structured telephone support (STS) or telemonitoring (TM) programmes for patients with chronic heart failure (HF) was published, followed by an update in 2010. [1, 2] The latter identified thirty RCT's (25 peer reviewed publications and five abstracts), including 9,806 patients. The main conclusion of this meta-analysis was that patients assigned to TM had lower all-cause mortality (RR 0.66, 95% CI 0.54-0.81, p<0.0001) and fewer HF-related hospitalisations (RR 0.79, 95% CI 0.67-0.94, p 0.008), while the effect of STS was limited to HF-related hospitalisations (RR 0.77 (95% CI 0.68-0.87), p < 0.0001). Criticisms included the methodological quality of individual studies, heterogeneity and potential publication bias.[3, 4] The subsequent publication of several large RCT's with neutral results in the following years resulted in growing uncertainty regarding the benefit of STS and TM.[5, 6] Based on these conflicting results, the 2012 ESC guidelines for the diagnosis and treatment of acute and chronic HF did not recommended widespread implementation of remote monitoring and called for more research.[7] In response to these recommendations from

the ESC, a further update of the Cochrane review was undertaken and published in the Cochrane Library in October 2015.[8]

The main differences between the 2015 and 2010 versions are: 1) inclusion of 17 new RCT's (41 in total, including 12,947 patients), 2) exclusion of abstracts (only completed studies published in peer-reviewed journals were eligible), 3) exclusion of the study by Kielbock et al. which was considered by some to be a cohort study open to bias rather than an RCT [4, 9], and 4) re-classification of a study that used interactive voice response technology as STS instead of TM.[10] The latest update of the Cochrane review again demonstrates that, compared to usual care, STS reduces all-cause mortality by 13% (95%CI 0.77 to 0.98) and heart failure-related hospitalisations by 15% (95% CI 0.77 to 0.93) and that non-invasive TM improves these outcomes by 20% (95% CI 0.68 to 0.94), and 29% (95% CI 0.60 to 0.83) respectively. These results confirm those reported in the previous Cochrane reviews and should encourage readers to put recent studies with a neutral outcome into perspective. More recent trials may have increased uncertainty but, overall, the balance of evidence still suggests that these interventions do reduce mortality and HF admissions.

In May 2016, the new ESC guidelines on diagnosis and treatment of acute and chronic heart failure were published.[11] These guidelines include a section on 'follow-up and monitoring', stating that "numerous prospectively initiated clinical trials (a.o. Tele-HF, TIM-HF, INH, WISH and TEHAF) including >3,700 patients have not confirmed clinical benefits of telemedicine in HF". Surprisingly, the recently published Cochrane review comprising data on >12,000 patients and >40 RCT's is not mentioned. Also, the magnitude of benefit of non-invasive TM is similar to that observed with some interventions that received Class I or IIa recommendations in the latest ESC guidelines. In our opinion, this is an important omission from the current guidelines [11] considering the esteem in which The Cochrane Collaboration is generally held.

The reasons for the fog that continues to surround the topic of remote monitoring in HF are multiple and include the use of different technologies for different types of patients (stable versus unstable), over different periods of time, in a different era (of background treatment) and with different comparators ("usual care" sometimes being enhanced to an unusual degree).

Of four different types of noninvasive remote monitoring technologies (STS, TM, videophone, and interactive voice response devices) only STS and TM appear effective in reducing the risk of all-cause mortality and heart failure–related hospitalizations.[12] The poor compliance associated with use of telephone-based interactive voice-response technology in the Tele-HF study is an important reason for the neutral result of this trial. [6] WISH, another neutral study, focused solely on weight monitoring, a variable that has a low sensitivity for detecting deterioration [13, 14]. Finally, TIM-HF was a well-designed and conducted RCT, but focused on stable, well-treated patients with HF who had low event rates.[5] Remote monitoring alone has no benefit; it can only improve patient outcomes by improving the delivery of interventions that modify outcome, for example ensuring safe implementation of target doses of HF medicines. Therefore, it is not surprising that TM has little impact on outcome in stable patients already receiving expert treatment. The TEN-HMS study nicely demonstrated that TM was associated with higher prescription rates of disease modifying medications, which may explain the positive effect on mortality observed in this trial.[15]

The Cochrane review has focused solely on non-invasive remote monitoring of patients with heart failure, but other meta-analyses have examined the effects of remote monitoring through cardiac implantable electronic devices (CIEDs). Individual studies have yielded conflicting results, but the overall conclusion of pooled data suggest that invasive monitoring reduces hospital visits (mainly planned visits), with no effect on cardiac hospitalisations and mortality.[16] The accuracy of CIED diagnostics in predicting worsening HF is fundamentally limited by the function of the device. Monitoring "device diagnostics" allow us to detect device malfunction early, to minimize the risk of

inappropriate shocks and to reduce the time to clinical decisions. However, this success has not yet been accompanied by a reduction in heart failure events, probably because many other aspects of the disease contribute to poor outcome.[17]

To summarize, RCTs of STS and TM in heart failure are not consistently positive but the bulk of evidence is in favour of a beneficial effect, both on overall mortality and HF-related hospitalisations. This has been shown by several Cochrane reviews, the most recent one being published only one year ago. Cochrane Reviews are internationally recognized as high quality work, and should not be omitted from current guidelines, especially when they provide interesting information and help to put individual trials into perspective. When access to specialist multidisciplinary heart failure programmes continues to be limited by barriers created by geography, healthcare systems and funding, it seems unwise to ignore evidence for a method of delivering an important clinical service to the most disadvantaged HF populations. Globally, many HF patients do not have access to specialized, face-to-face heart failure care; remote monitoring can help compensate for this.

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Table 1

Cochrane review	Era	Included trials (n)	Mortality	HF-related hospitalisations
2007	1966-2006	14		
TM			RR 0.62 (0.45-0.85)	RR 0.86 (0.57-1.28)
STS			RR 0.85 (0.72-1.01)	RR 0.78 (0.68-0.89)
2010	1966-2008	30		
TM			RR 0.66 (0.54-0.81)	RR 0.79 (0.67–0.94)
STS			RR 0.88 (0.76-1.01)	RR 0.77 (0.68–0.87)
2015	1966-2015	41		
TM			RR 0.80 (0.68- 0.94)	RR 0.71 (0.60- 0.83)
STS			RR 0.87 (0.77- 0.98)	RR 0.85 (0.77 -0.93)

Table 1. Summary of main characteristics of the Cochrane reviews of 2007, 2010 and 2015 on structured telephone support or non-invasive telemonitoring for patients with heart failure. TM = telemonitoring; STS = structured telephone support; HF = heart failure; RR = risk ratio. Risk ratios are presented with the corresponding confidence interval.